Further, the examiner is thanked for the courtesies extended to the undersigned during an April 17, 2002 telephonic interview, at which time the Section 112, second paragraph, rejection was discussed.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1, 2, 4, and 5 were rejected under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim that which Applicants regard as the invention. In particular, the examiner took issue with the description of the fused ring systems in the claimed compound. The examiner argued that

> [i]t is not seen how ortho monovalent groups such as alkyl, alkoxy . . . alkylamino can even form rings when there is no remaining available bond in any of these groups. The examiner has repeatedly indicated the 2 ring systems that are clearly indicated at this location. There is nothing else in the specification that provides further guidance. (December 31, 2001 Official Action at 2.)

Without conceding the propriety of the rejection, Applicants have amended claim 1 to refer to B as either a phenyl ring or a fused bicyclic ring, wherein the fused bicyclic ring consists of a phenyl ring and an aromatic ring fused to the phenyl ring, wherein the aromatic ring is optionally substituted with one or more heteroatoms selected from O, N, or S.

Support for this amendment can be found in the subject specification at page 5, lines 21-24, and in Examples 2 and 16. Specifically, at page 5, the subject specification states that

> When B comprises an aryl group, two substituents on the aromatic ring may be connected together to form another ring system. For example, B may be a benzodioxanyl ring. Preferred groups at variable B are monocyclic aryl or bicyclic heteroaryl groups. Most preferred at B are an alkoxyphenyl or a bicyclic heteroaryl group containing one heteroatom.
>
> The term heteroaryl group includes a mono or bicyclic aromatic group containing one or more heteroatoms (e.g., nitrogen, oxygen, sulfur) which contain 5 to 12 ring atoms. When it is specified that when any of Ar, Ar', or B is heteroaryl, any of nitrogen, oxygen, or sulfur can be present in the heteroaryl group only once, it means that the term aryl ring system will have only one occurrence of a given heteroatom. Thus, e.g., thiazolyl and isoxazolyl groups are not excluded from the scope of the claims by such a proviso, but, e.g., imidazolyl and pyrimidinyl groups would be excluded from the scope of the claims with such a proviso.

Further, Examples 2 and 16 describe the preparation of compounds that fall within the scope of amended claim 1 wherein B is a bicyclic heteroaryl group i.e., benzodioxanyl or indolyl groups. Thus, the specification clearly supports the amendment to the claims, as it describes bicyclic fused ring systems containing a phenyl ring fused to an aromatic ring, wherein the aromatic ring is optionally substituted with N, O, or S.

During the April 17, 2002 interview, the examiner indicated that the claims should be limited to only those fused ring systems specifically disclosed in the specification, i.e., indolyl and benzodioxanyl groups. This argument is echoed in the official action, wherein the examiner commented that there is nothing in the specification that provides guidance for fused ring systems beyond the two ring systems that are specifically disclosed.

Applicants respectfully disagree. First, Applicants note that the rejection is under the second paragraph of §112, rather than the first paragraph, and therefore, the examiner's argument concerning the scope of the claims is not applicable. However, even if a written description and/or enablement rejection were at issue, Applicants have complied with the first paragraph of Section 112, as well as with the second paragraph of that section of the patent statute. In order to support generic claims involving chemical materials, the generic formula should indicate with specificity what the generic claims cover so that one skilled in the art can identify many of the species that the claims encompass. *Regents of the University of California v. Eli Lilly & Co.,* 119 F.3d 1559, 1568 (Fed. Cir. 1997). Applicants have complied with that requirement. Applicants have amended the claims to specifically refer to fused bicyclic ring systems comprising a phenyl ring and an aromatic ring, optionally substituted with a heteroatom. This claim language clearly illustrates the genus that is encompassed by the claims, especially when the claims are read in light of the specification (including the excerpts provided above and the specific examples of the claimed genus provided in the Examples). Thus, the claims should not be limited to only those specific embodiments disclosed in the specification, and Applicants respectfully submit that the rejection is untenable under either paragraph of Section 112.

In view of the amendment to claim 1 and the accompanying remarks, favorable reconsideration and withdrawal of the Section 112, second paragraph, rejection are earnestly solicited.

Rejection Under 35 U.S.C. § 103(a) Over Shiota

Claims 1, 2, 4, and 5 were rejected under 35 U.S.C.§ 103 as unpatentable over Shiota (WO '329). The examiner argued that Shiota was published within a year of the filing date of the instant application and that Shiota discloses compounds similar to those of the instant claims which are used to treat arthritis. The examiner reasoned that

> [w]hile these compounds do not anticipate the instant scope because of the presence of the methylene between phenyl and piperazine ring, they are obvious variants since the reference also teaches direct attachment of said phenyl ring. . . . Thus, it would have been obvious to one skilled in the art at the time the invention was made to remove the methylene in the aforementioned compounds and thus obtain [the] instant compounds . . . as taught by Shiota. (December 31, 2001 Official Action at 4).

Applicants respectfully traverse this rejection. Shiota was published on November 27, 1997. However, the instant application was filed on July 31, 1998 and after
claims priority from USSN 60/070,269, filed December 31, 1997 and Italian Patent
Application SN M197-A-001861, filed August 1, 1997. → IVO English translation provided.

Therefore, Shiota is not available as prior art because it was published after the earliest effective filing date of the instant application. Favorable

reconsideration and withdrawal of the rejection based on Shiota are respectfully requested.

Rejection Under 35 U.S.C. § 103(a) Over Janssen

Claims 1, 2, 4, and 5 were rejected under 35 U.S.C. § 103(a) as unpatentable over Janssen, U.S. Patent No. 3,030,367 ("Janssen"). The examiner contends that

> Janssen teaches similar compounds to that claimed for use as analgesics, and appetite suppressants. While said compounds (egs. 1-4) do not anticipate the claims in view of proviso (1), they are obvious variants as they only differ in being unsubstituted in one of the phenyl rings vs. instant Me (i.e. alkyl) substituted phenyl. H v. Me is not considered a patentable advance absent evidence of superior, unexpected results. . . . Thus it would have been obvious to one skilled in the art at the time the invention was made to expect compounds claimed herein that are methylated on . . . one of the phenyl rings to also possess the uses taught by the art in view of the close structural similarity outlined above. (December 31, 2001 Official Action at 4).

Applicants respectfully disagree. The compounds of the present invention are used to treat disorders of the lower urinary tract, including disorders associated with neuromuscular dysfunction, such as urinary urgency, increased urinary frequency, incontinence, urine leakage, enuresis, dysuria, urinary hesitancy, and difficulty in emptying the bladder (Specification at 4, lines 11-15). The compounds of the invention are also used to treat CNS disorders associated with serotonergic dysfunction, such as anxiety, depression, hypertension, sleep/wake cycle disorders, feeding behavior, sexual dysfunction, and cognition disorders (Specification at 4, lines 16-20).

In contrast, Janssen suggests that the compounds are useful as analgesics and appetite suppressants. There is no teaching or suggestion in Janssen that the compounds may be used to treat disorders of the lower urinary tract or the CNS, as disclosed in the instant application. It is well settled that a *prima facie* case of obviousness may arise among chemical compounds having close structural similarity and similar utility. *In re Payne*, 606 F.2d 303 (CCPA 1979) (holding that "[a]n obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." Applicants have clearly disclosed compounds having different structures and function and there is no motivation in Janssen to modify the compounds disclosed therein to derive the instantly claimed compounds.

The examiner relies on *In re Wood* and *In re Lohr* to support the instant obviousness rejection. However, this case is different than the scenarios presented in *Wood* and *Lohr*. Briefly, both *Wood* and *Lohr* relate to the CCPA's finding of obviousness of methyl-substituted compounds based on prior art references teaching the corresponding unsubstituted compounds having the same utility as that which was claimed for the methyl-substituted compounds. In both cases, the court upheld the obviousness of methyl-substituted aromatics in view of the prior art unsubstituted aromatics having the same properties and utilities. However, these cases are not

entirely on point because the instantly claimed compounds do not have the same properties or utilities as the Janssen compounds.

In this regard, the examiner's attention is directed to *In re Wagner*, 372 F.2d 877 (CCPA 1967), wherein the court reversed a PTO conclusion of obviousness premised primarily on structural similarity. In *Wagner*, the claims recited benzimidazole derivatives substituted with at least one lower alkyl group at two specific positions and the prior art taught benzimidazole derivatives having no substitutions at these positions or bearing dimethyl substitutions at two other positions of the benzimidazole ring. On appeal, the CCPA specifically rejected the PTO's conclusion that "the modification of a compound by the addition of one or more methyl groups is well known and thus obvious," noting that the PTO failed to consider the biological properties of the compounds and focused instead on mere homology. *Id* at 881. Moreover, in *In re Cescon*, 474 F.2d 1331, 1334 (CCPA 1973), citing the decision in *Wagner* and *In re Larsen*, 292 F.2d 531, 533 (CCPA 1961), the CCPA held that if

> **there was nothing [in the prior art] to indicate that the compounds, when made, would have these properties, it was not obvious to make the** ~~compounds. In such a case the allowance~~ of claims to the compounds must depend on the proposition that it was unobvious to conceive the idea of producing them, within the meaning of Title 35 U.S.C. § 103.

Therefore, Applicants respectfully submit that the rejection based on Janssen should be withdrawn. The claimed compounds have completely different biological properties than the Janssen compounds and there is nothing in Janssen to indicate that the compounds, when made, would have these properties; it was

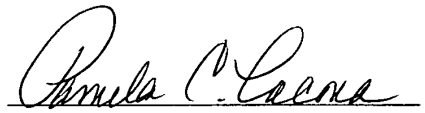
therefore, not obvious to make the instantly claimed compounds. Favorable reconsideration is requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the claims are in condition for allowance and such action is earnestly solicited.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Leonardi, Amedeo; Motta, Gianni; Riva, Carlo; Testa, Rudolfo

Serial No.: 09/127,059 Art Unit: 1624

Confirmation No.: 9662

Filed: July 31, 1998 Examiner: E. Bernhardt

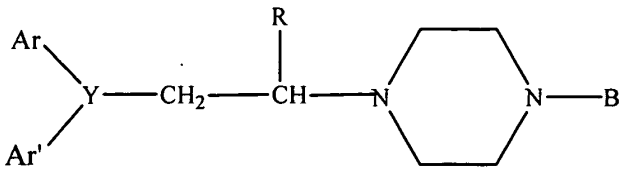
For: DIALKYLPIPERAZINES ACTIVE ON THE LOWER URINARY TRACT

MARK-UP FOR AMENDMENT OF DECEMBER 31, 2001
PURSUANT TO 37 C.F.R. § 1.121

Assistant Commissioner for Patents
Washington, DC 20231

IN THE CLAIMS

(Amended) A compound of the formula



wherein

each of Ar and Ar′ is independently [chosen] selected from a group consisting of phenyl and pyridyl each optionally substituted by one or more members selected from the group consisting of alkyl, alkoxy, cyano, nitro, amino, alkylsulfonylamino, or alkylamino;

Y is [chosen] selected from the group consisting of a nitrogen atom, a CH, C-OH, C-CN, or a C-$CONH_2$ group;

R is a hydrogen atom or a lower alkyl group;

B is (a) phenyl, optionally substituted by one or more [members] substituents selected from the group consisting of alkyl, alkoxy, halogen, cyano, nitro, amino, alkylsulfonylamino, and alkylamino; [wherein when the phenyl ring is substituted with two members of the group consisting of alkyl, alkoxy, amino, alkylsulfonylamino or alkylamino, and the two members are adjacent to each other, the substituents may be connected together to form a ring fused to the phenyl] and (b) a fused bicyclic ring system comprising a phenyl ring and an aromatic ring fused to said phenyl ring, wherein said aromatic ring is optionally substituted with one or more heteroatoms selected from N, O, or S, with the provisos that

1) when B is methoxyphenyl and Y is [any] selected from [of] C-CN[,] and C-$CONH_2$, then Ar and Ar' are not simultaneously unsubstituted phenyl;

2) when Y [equal] is CH, Ar and Ar' cannot both be optionally substituted pyridyl;

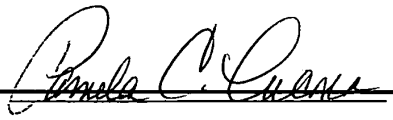
3) when Y [equal] is CH and one of Ar and Ar' [equal] is optionally substituted phenyl, the other of Ar' and Ar cannot [equal] be optionally substituted pyridyl; and

4) when Y [=] is CH or a nitrogen atom and each of Ar and Ar' are optionally substituted phenyl wherein said substitution is methyl, then B cannot be unsubstituted phenyl,

and enantiomers, diastereomers, N-oxides crystalline forms, hydrates and pharmaceutically acceptable salts thereof.

Respectfully submitted,

Dated: April 29, 2002



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